RECOMMENDATIONS FOR EVALUATING THE SAFETY OF IRRADIATED FOODS

FINAL REPORT

JULY 1980

Prepared for the Director, Bureau of Foods, FDA

MEMBERSHIP OF THE IRRADIATED FOOD COMMITTEE

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INTRODUCTION AND BACKGROUND

The Irradiated Foods Committee was authorized on September 10, 1979 and established on October 23, 1979 to provide a total reassessment of all relevant issues applicable to irradiated foods. Since that time the Committee has become acquainted with the subject and accompanying problems by reviewing the relevant literature, interviewing appropriate FDA personnel and international experts knowledgeable in the area of radiation chemistry and toxicological evaluation (see Appendix I).

The Committee was charged with the following tasks:

1. To review current policy.
2. To examine the foundation and soundness of that policy and its past implementation, and
3. To establish those toxicologic requirements appropriate for assessing the safety of irradiated food consistent with the level of human exposure, where the degree of testing is consistent with the potential risk as predicated on the level of human exposure. These requirements would be analogous to, and consistent with, the philosophy supporting the Cyclic Review of direct additives.

The Committee emphasizes that this report is a policy recommendation and <u>not</u> a petition, petition guideline, FEDERAL REGISTER (FR) document, or a comprehensive review of all data submitted to FDA and all available scientific literature. We forsee the development of guidelines for petitioners and a FR document as tasks of future committees.

The intended technical effects from exposure of food to ionizing radiation include: sprout inhibition, insect control, and the different food preservation modes which involve various levels of microbial destruction. These applications extend from low doses for limited shelf-life extension to high doses for complete sterilization of foods (Figure 1). It is noteworthy that existing alternative methods for achieving these effects in foods require the use of a variety of chemical and physical means. The versatility of irradiation can be seen from the variety of applications. Irradiation may be used as a substitute for food additives (nitrite), fumigants (ethylene dibromide, ethylene oxide), plant regulators (maleic hydrazide), and as a food processing technique for food preservation (canning, pasteurization).

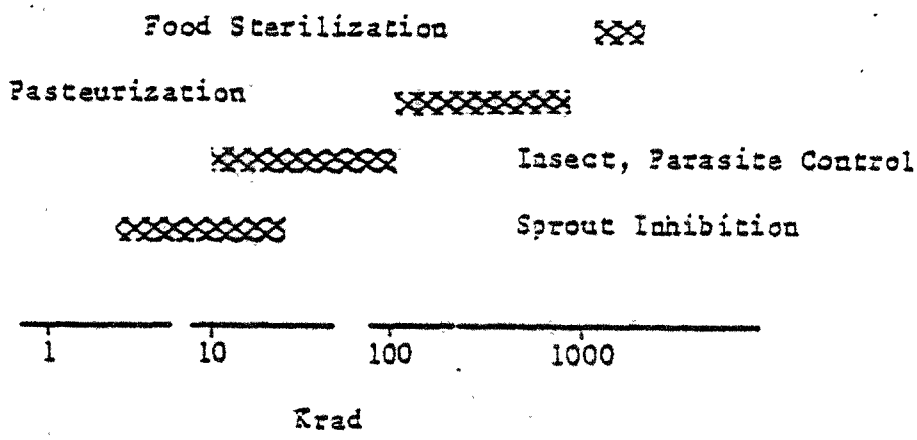


Figure 1 - Categories of intended use for food irradiation.

Because of these differing applications, questions have arisen regarding which provisions of the Federal Food, Drug, and Cosmetic Act are relevant to irradiated foods. Regardless, of whether one considers the source of radiation as an unsafe "food additive," or whether the food is adulterated because of exposure to radiation, or whether irradiation is viewed as a process, the safety requirements for irradiated foods remain the same.

Microbiological concerns for the safety of irradidated foods are substantially the same as those for other methods of food preservation as expressed in the Bureau's 1967 Staff Seminar Report: Radiation Application to Food[1] and Joint FAO/IAEA/WHO Expert Committee Report: Wholesomeness of Irradiated Food[2]. For example, the traditional heat processing of canned foods to provide a sterile, shelf-stable food is based on a specific thermal kill criterion for Clostridium botulinum spores. This criterion requires that the heat processing reduce the original spore count by twelve log units ("12D process"). The parallel process utilizing radiation sterilization of foods (radappertization) is evaluated by the same standard of efficacy as the conventional thermal processes. The 12-D dose varies with the particular food irradiated; for pork, beef, and chicken this dose has been found to range from 2.4 to 4.5 Mrads and defines, in each case, the "sterile dose."

From a number of studies on the radiation stability of vitamins, proteins, fats and other nutrients, it is known that several nutrients are sensitive to degradation by ionizing radiation (see also Appendix II). This sensitivity, however, depends not only upon the nature and composition of the food system, but also on a number of controllable factors such as the dose, characteristics of the radiation used, temperature of the product being irradiated, and the relative presence or absence of oxygen in the product environment during irradiation. Hence, the destruction of labile nutrients can be minimized by careful selection of the conditions for irradiation. Some of the macronutrient components - amino acids such as cystine, methionine and tryptophan, for example - are more sensitive to irradiation than others. The amounts that are destroyed, however, are usually insignificant compared to the unirradiated food or to a product treated by a conventional process. Criteria for the safety evaluation of the nutritional adequacy of irradiated foods, are essentially identical with those expressed in the 1967 report. When irradiation results in the significant loss of important micronutrients, enrichment may be considered appropriate.

For past safety evaluation, toxicological indices and protocols were applied to irradiated foods as if the whole irradiated food was a discrete chemical entity similar to a "conventional" food additive. It was recognized that there were problems associated with such studies. The most significant of these problems was to achieve dietary concentrations of the food additive in the animal tests which would be multifold exaggerations of concentrations to which humans would be exposed. Many

foods constitute a significant percentage of the human diet (see Appendix III) and significant exaggeration of these cannot be obtained without disturbing the nutritional balance of the laboratory test animal. Solutions to these problems were not readily available with the state-of-the-art in toxicology and in the chemistry of irradiated foods at that time. Significant progress had been made in both of these areas in the ensuing years as will be discussed.

Toxicology is an applied and integrative science and it's progress relies on the development of new information in the basic sciences, improvements in test protocol design and execution, as well as on the continually growing volume of information on the toxicology of a variety of chemical classes. Our understanding of the molecular changes underlying many gross toxic effects has increased immensely since 1967.

Because of the increased public awareness of potential harm from the growing number of chemicals in the human environment, there has been an impetus towards the development of new and improved toxicological tests. The area that has received the greatest attention over the past ten years has been the development of short-term tests for detecting chemicals with mutagenic activity. The initial reason for the development in this area stemmed from the concern that chemicals would cause mutations that would be deleterious and thereby increase the burden of inherited diseases in future generations. More recently, the high costs (both money and time) involved in obtaining data from mammalian bioassays have motivated the development of more rapid methods for detecting chemical carcinogens. The empirical demonstration of a high correlation between mutagenicity and carcinogenicity is a sufficient basis for establishing a role for

mutagenicity testing as a predictive tool for carcinogenicity. That there is evidence for a mutational component in some types of cancer (retinoblastoma, malignant melanoma, etc.) lends additional credibility to the predictive use of such tests.

Much has been written on the current status of the various toxicological tests and strategies of their employment. Because of the general awareness of this progress within the scientific community an additional comprehensive review of the state-of-the-art in toxicology was considered unnecessary by the Committee. Certainly, it has been necessary for the Committee to become aware of the current procedures. In this context, we consulted with Bureau staff who are involved in the Sensitivity of Method (SOM) and Cyclic Review documents, as well as examined the toxicological tests currently being used by the International Project in the Field of Food Irradiation.

RADIATION CHEMISTRY

As a basis for further discussion and to clearly outline the reasons for reliance on the results of chemical analyses of radiolytic products as an important factor in safety evaluation, key features of food irradiation chemistry will be reviewed. This review will briefly consider the significance of each characteristic of radiation as it defines or limits the changes brought about in food or food components. More detailed discussions of these issues are available in the scientific literature[3].

Ionizing radiation is, in comparative terms, high energy. Radiation quanta in this part of the electromagnetic spectrum are measured in millions of electron volts. The energy source for irradiating foods may be a decaying radioactive nuclide or a machine-generated electron beam at energy levels below 10 MeV. Since a photon energy of 10 MeV is near the minimum level required to induce radionuclides, there is no significant radioactivity above that due to naturally occurring isotopes induced in irradiated food[4]. Both radiation sources result in essentially the same scheme of chemical events in irradiated food. Of particular interest is the absolute amount of energy absorbed by food. This absorbed energy is the quantity which establishes the net potential for molecular alteration, regardless of how energetic the source emissions are.

Total absorbed energy is expressed as radiation dose, typically in rads or grays. A rad is defined as 100 ergs/gram or 10^{-2} joules/kg. The new international unit of radiation dose is the gray (Gy) which equals 100 rad. (The more familiar unit "rad" is used in this report.)

It should be emphasized that the total energy absorbed is small for even the largest anticipated doses (sterilization of red meat). For example, if all the energy absorbed in a one megarad (1 Mrad) dose were converted to heat energy the sample temperature would rise only 2.4°C per unit weight, assuming the food sample had the heat capacity of water (1 cal/°C). This is about 3.3 percent of the energy needed to raise the temperature of water from room temperature to its boiling point. On a unit weight basis then, these radiation energies are much less than those absorbed in cooking.

Ionizing radiation results in the formation of free radicals, which are characteristically unstable and very reactive chemical intermediates. Free radicals in food are initiated either directly by interaction with high energy electrons, or indirectly, primarily by reaction with hydroxide radicals and low energy solvated electrons. These latter two species result from the radiolysis of water and are the primary radical initiating agents responsible for the formation of most of the subsequent radiolysis products. Consequently, the amount of water in a given food and the extent of hydration of various food molecules has a profound influence on the quantitative and qualitative aspects of the radiolysis yield.

Most free radicals are short-lived intermediates; their intrinsic reactivity ensures that they will normally react within fractions of a second after their formation to form more stable molecules. Free radicals with half-lives of minutes are not uncommon particularly at low temperatures and in environments which limit their diffusion. Free radicals are not entirely indiscriminate in selecting a reaction pathway

to an end product. The actual mechanistic pathway is influenced by conventional chemical factors such as concentrations of possible reactants, the relative rate constants for competing reactions, and the mobility of the radicals. As a result, these parameters confer considerable mechanistic selectivity to a given radical and serve to constrain and therefore limit the types of resultant, stable radiolytic products (RPs) formed.

RADIOLYSIS PRODUCTS IN FOOD

The chemistry of foods, isolated food components, and various model food systems exposed to ionizing radiation has been extensively investigated, especially in an attempt to identify the RPs formed. Foods, both irradiated and unirradiated, are chemically complex and may contain hundreds of discrete chemical species. Since many of these compounds are present in the low ppm (or ppb) range, the complete chemical characterization of food is technically not feasible. Hence, while the radiolysis data available in the scientific literature are insufficient to completely catalog the identity and quantity of each RP formed in any particular irradiated food, this body of data circumscribes the type and amount of radiation chemistry which is likely to occur in foods. The estimation of the following two factors are of prime importance in proceeding with a rationale for the safety evaluation of irradiated foods.

A. The probable total yield of RPs in food as a function of absorbed radiation dose, and

B. Some assessment of the fraction of these RPs which are unique radiolytic products (URPs) to the irradiated food.

TOTAL RADIOLYTIC PRODUCTS

The quantitative yield of RPs in food is primarily a function of the magnitude of the absorbed radiation dose. However, secondary factors such as food temperature, composition, viscosity, and environment are recognized as important to the quantity and type of RPs formed. These latter parameters can often be controlled and optimized to provide the most desirable product.

The amount of radiation absorbed remains the first criterion however, in determining the amount of radiation chemistry which occurs. Results from the Army's high dose program on high protein meats, as well as those from numerous model systems, show that radiolysis yields may be characterized as generally increasing linearly with absorbed dose. In addition, based on the energetics of ion pair production, the yield of new species formed (equivalent to RPs) can be calculated from the following expression:[5]

$$\text{Yield (in mmol/kg)} = \text{Dose (krad)} \times G \times 10^{-3}$$

where G is the number of molecules formed or destroyed per 100 eV absorbed.

It has been shown that G-values determined from the irradiation of individual compounds in solution, or from the irradiation of simple mixture (model systems), can be used to predict the total G-value in the actual food matrix[6].

The utility of G-values for estimating yields in irradiated foods is enhanced by the discovery that individual food components tend to produce the same radiolysis products when isolated, or when occuring as natural components of complex foods[7]. Army research workers at the Natick

Laboratory have found that, qualitatively, the RPs formed from the lipid fractions of beef, chicken, and pork are largely similar. The quantities of these RPs are dependent only on the proportion of fat in the irradiated meat. Expected cross-over RPs are thus minimal; for example, the reaction between lipid-derived and protein-derived free radicals are found to be limited by reactions occurring across interfacial regions between tissue phases in meat. This apparent "compartmentalization" of food components considerably restricts the spectrum of possible RPs likely to occur within or across classes of foods. Thus, foods of similar chemical composition, irradiated under similar conditions, will contain RPs derived from common precursors and such irradiated foods may reasonably be viewed in a generic sense.

For purposes of estimating the total levels of RPs in food, a value of G_T=1 has been selected. The results noted above, as well as those from the Natick Laboratory,[7] suggest that if food irradiation practices result in an organoleptically acceptable product, the actual G_T will be adequately characterized by this value. In practice, with various foods and conditions, this factor may at times be greater or less than one, but current information supports unity as a reasonable policy-making assumption. Variations of G_T of plus or minus 100% should not significantly alter the arguments based on an assumed value of G=1. Therefore, as indicated by the above equation, a dose of 1 Mrad will yield 1 millimole of total RPs per kilogram of irradiated food. Assuming an average RP molecular weight of 300, one kilogram of food irradiated at 1 Mrad will contain only 300 mg of newly formed chemicals.

TABLE 1

ESTIMATES OF RADIOLYTIC PRODUCTS IN IRRADIATED FOODS

Radiation Dose (krad)	G_T (Events/100eV)	(a)Yield of all RPs in Food (mmol/kg)	Yield of all RPs if MW=300 (mg/kg)	(b)Yield of URPs (mg/kg)
10	1	0.01	3	0.3
50	1	0.05	15	1.5
100	1	0.10	30	3.0
1,000	1	1	300	30

(a)-Yield (in mmol/kg) = Dose (krad) x G_T x 10^{-3}
(b)-Assumes only 10% of RPs are unique (see text)

UNIQUE RADIOLYTIC PRODUCTS

While the yield of total RPs from a given irradiation dose may be substantial in toxicological terms, only unique radiolytic products (URPs) should be of concern. For example, increases in the fatty acid or amino acid content of a food due to the radiation induced break-down of triglycerides and proteins simply increase the amount of food constitutents normally present.

Unique radiolytic products, although defined here as substances not found in the unirradiated food, may also be common constitutents in the human diet. The true extent of the dietary "uniqueness" of URPs is somewhat tenuous, due largely to the paucity of information on the composition of both processed and unprocessed foods at the parts per million level. It is quite possible that radiolytic compounds now classified as unique in irradiated foods also occur in foods which have been processed by conventional thermal methods. Examination of the most complete set of available data on RPs in food will serve to illustrate and document the significance of distinguishing between total RPs and URPs. The U.S. Army's high-protein food sterilization program provides detailed

analysis of volatile species identified in raw beef irradiated at 5 Mrad[8,9]. These volatiles consist of a nearly homologous series of 65 RPs derived primarily from the radiolysis of the triglycerides from the beef lipid fraction. Of the 65 volatiles, 23 were also identified in the thermally sterilized control, so that 42 were unique to the irradiated product (URPs). However, of these 42 URPs only six could not be identified in the volatile fractions of other nonirradiated foods[10]. Thus, only some 10% of this particular subset of RPs (the 65 volatiles) are in fact URPs. The structures of these six URPs are typical of the molecules identified as occurring in other food volatiles, and are similar to natural food consitituents.

Although, this example is taken from a series of RPs which happen to be associated with a volatile fraction of irradiated food, there is no apparent reason to believe that they do not also typify the relationship of <u>non-volatile</u> RPs and URPs to one another, and to the fraction of RPs which are consitutents to be found in other non-irradiated foods. Certainly some URPs will be formed which are structurally atypical of parent food molecules. Such URPs may be free radical coupling products of lipid and protein derived radicals, forming various coupling compounds, dimers, and cross-linked products. However, enzymatic hydrolysis by digestive enzymes is expected to process the majority of such URPs to yield normal molecular subunits, such as the fatty acids, amino acids, monosaccharides, and further subunits of these components, which would have resulted from the normal digestion of the orginal parent molecules.

Additionally, comparisons have been made on the types of RPs formed in irradiated fats with the thermal products formed in heated or thermally oxidized fats. These studies also indicate considerable product similarities. Thermal decomposition products from fatty acids, triglycerides, and fatty acid methyl esters produce a spectrum of n-alkanes, 1-alkenes, ketones, aldehyes, lactones, dimeric hydrocarbons, alcohols, CO_2, CO, H_2, and dimer acids and esters[11]. The dimeric compounds identified in heated methyl oleate were found to be structurally quite similar to dimers produced by irradiation of potassium oleate.

From the above considerations, it is reasonable to assume that the URPs constitute 10 percent or less of the total radiolytic product yield. The last column in Table 1 shows the expected quantity of total URPs at various irradiation doses.

1980 POLICY RECOMMENDATIONS

The Committee's main task was: to establish those toxicologic testing requirements appropriate for assessing the safety of irradiated food, where the degree of testing is compatible with the potential risk as indicated by the level of human exposure. Based on what we have learned from our review of all aspects of food irradiation, it is apparent that any toxicological testing requirements must also be predicated on the amounts of new chemical constituents generated by the irradiation process (URPs). Hence, the components of any new policy for assessing the safety of irradiated food are: 1) projected levels of human exposure; 2) qualitative and quantitative estimates of URPs; and 3) state-of-the-art sensitive toxicological tests.

While numerous efforts to estimate food consumption have been made, it is generally recognized that no single approach provides sufficiently accurate data. Hence, our projection of human exposure to irradiated foods will necessarily suffer the same limitations. The committee utilized estimates of a) total food consumption, b) dietary items proposed for irradiation and, c) the percent of each dietary item which may be irradiated. (See Human Exposure, Appendix III). These factors will vary with the specific food under consideration; however, a rough estimate based on these factors suggests that 10% of the total diet may consist of irradiated food in the near future.

Calculations based on radiation chemistry clearly indicate that irradiation doses of 100 krad or less yield a concentration of total radiolytic products in food that is so limited that it would be difficult to detect and subsequently measure potential toxicological properties. In addition, at this dose unique radiolytic products will be on the order of 3 ppm, and since the number of individual URPs is likely to be greater than ten, the amount of any particular URP will be considerably less than 1 ppm. Finally, our estimates of URPs may be exaggerated.

Hence, because of the low level of total unique radiolytic products produced, it is concluded that food irradiated at doses not exceeding 100 krad is wholesome and safe for human consumption. This rationale is based solely on an estimate of the concentration of individual URPs produced by the radiation dose to the food, and pertains even if a high proportion of the total human diet is irradiated at 100 krad. However, there are foods, such as spices, which comprise only a fraction of a percent of the human diet. It can be calculated that a food which comprises 0.01 percent of the diet and is irradiated at doses up to 5 Mrad will contribute radiolytic products to the daily diet at a level lower than a food comprising a significant fraction of the diet and irradiated at 100 krad (see Table 1). Consequently, foods comprising no more than 0.01 percent of the daily diet and irradiated at 5 Mrad or less will also be considered to be safe for human consumption without toxicological testing. This recommendation based on anticipated levels of human exposure, is consistent with the charge to the Committee.

The proposed general policy concerns the single irradiation of food commodities. Selected instances of food irradiation may present novel considerations: for instance, a petition for a processed food may be received where one or more of the constituent raw commodities has been previously subjected to irradiation. Since it not possible, at this time, to predict the situations where such conditions may occur, they must be considered on a case by case basis.

TESTING

Foods irradiated at doses above 100 Krad and comprising more than 0.01% of the diet are estimated to contain URPs in sufficient quantity to warrant toxicological evaluation. The non-mammalian mutagenicity tests offer a level of sensitivity not practically attainable in whole animal tests, and recalling that many URPs may be similar chemically to substances occurring naturally in foods, these tests are considered appropriate tools to evaluate the potential carcinogenicity of irradiated foods. The tests recommended are 1) gene mutations in bacteria, with and without metabolic activation, 2) gene mutations in cultured mammalian cells, 3) DNA repair in mammalian cells, and 4) recessive lethal mutations in Drosophila. These test are considered to be the minimum battery. Requests for substitutions for any of the above tests should be justified and will be considered on a case by case basis.

Because of the anticipated low level of individual radiolytic products present in the whole irradiated food, the above tests must be performed on extracts in which the concentration of radiolytic products is maximized. Also, many of the radiolytic products from polysaccharides and proteins will be large molecules and will not penetrate the cell membrane in the in vitro systems, hence the use of enzyme digests is recommended prior to the concentration of URPs.

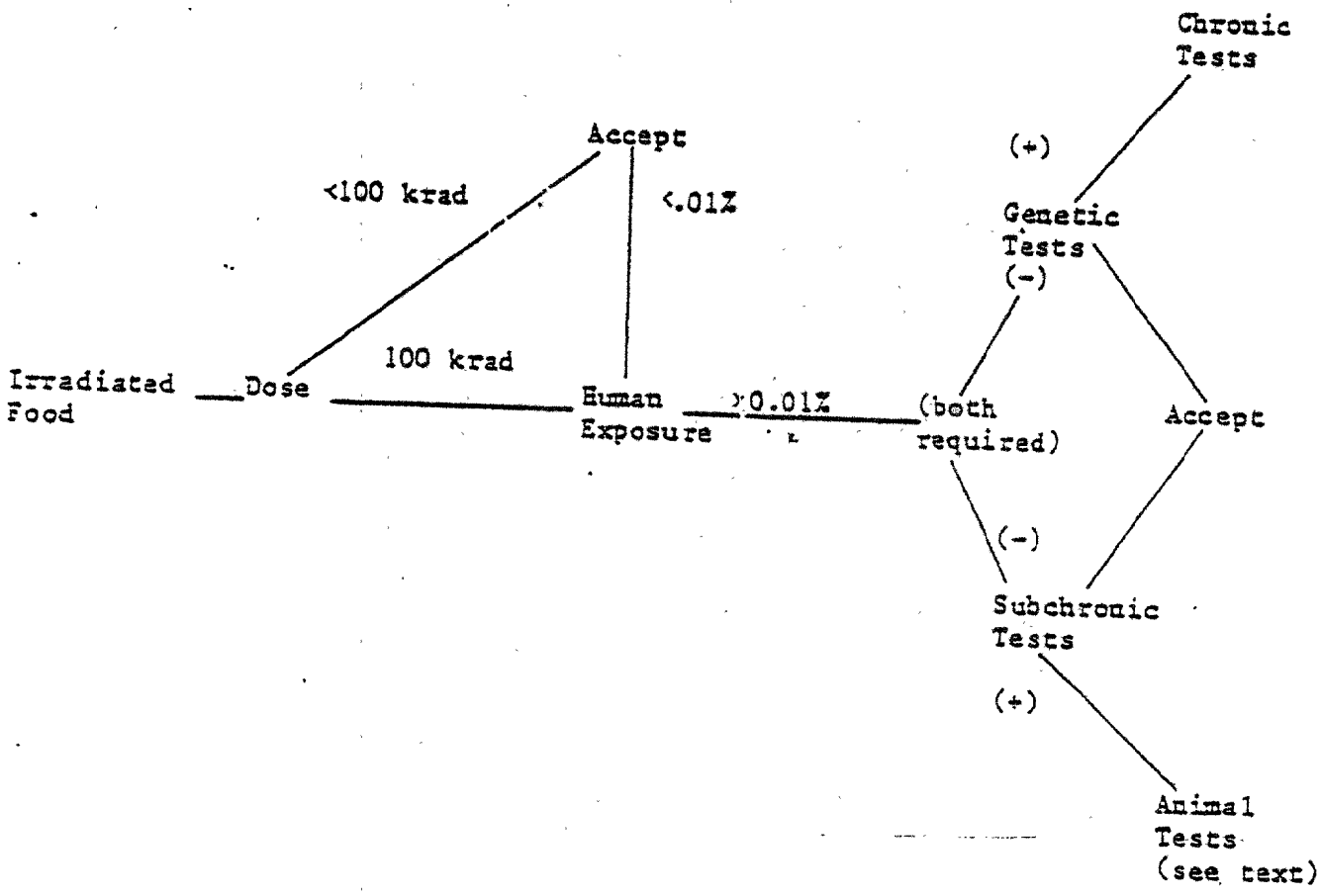
In addition to the short-term mutagenicity tests, foods irradiated at doses above 100 krad must be evaluated in 90-day feeding studies in two species (one rodent, one non-rodent). The 90-day rodent test should include *in utero* exposure. To assure that the test animals are exposed to the highest concentration of radiolytic products possible, the irradiated food may be lyophilized and incorporated into the animal diet at the highest concentration that does not compromise the nutritional requirements of the test species (see Appendix IV). It is not necessary to test enzyme digests of the irradiated food in these tests since each test animal provides digestion of food components before systemic absorption occurs. Higher doses of particular radiolytic products may be obtained if the selectively extracted and concentrated material used in the short-term tests is employed; however, it is recognized that much greater quantities would be needed for *in vivo* testing and thus would make this latter suggestion extremely difficult and expensive to effect in any practical sense.

CRITERIA

Unequivocal negative responses in the required tests will be sufficient to establish the safety of the irradiated food under test. Positive responses obtained in either or both of the types of required tests may trigger additional evaluation. Positive mutagenic responses suggest potential carcinogenicity and hence would necessitiate the performance of the chronic mammalian bioassay tests. The minimal requirements for positive mutagenic effect is the observation of positive responses in at least two of the short-term test systems. The rationale for requiring two positives is to reduce the probability of conducting further tests on the basis of a false positive or a species specific response. The results obtained in the chronic tests would either confirm or negate the positive results obtained in the short-term tests battery regarding the carcinogenic potential of the irradiated food; and, the results obtained in the chronic tests would be considered to be definitive.

In the 90-day studies, a variety of toxicological endpoints are evaluated and it is not possible a priori to determine what follow up tests may be required. Such decisions can only be made upon evaluation of actual test results. If the results obtained from the studies indicate teratological or reproductive effects, then the irradiated food must undergo teratological testing and/or reproductive testing via a three generation reproduction study. The overall procedures for establishing the safety of an irradiated food is displayed in Figure 2.

Figure 2 Safety Decision Tree



GENERIC

The earlier section on radiation chemistry discussed the generalization that the RPs formed are more a function of the chemical composition of the food than the irradiation dose. Thus, foods of a similar chemical composition would be expected to generate structurally similar radiolytic products. Therefore, when two or more foods are of sufficient similarity with respect to both chemical composition (lipids, carbohydrates, proteins and water content) and conditions of irradiation, they may be viewed in a generic sense for regulatory purposes. Comparability of radiation conditions is dependent upon the respective radiation dose, product temperature and ambient atmosphere during irradiation. Hence, toxicologial data obtained from a given irradiated food item may be applicable for another irradiated food in the same generic class. In addition, safety data collected from food irradiated at high doses are applicable to members of the same generic class receiving a lower dose[12].

This generic policy is an extension of the principles set forth in the general policy for evaluating the toxicity of irradiated foods and is based upon the significant research which has been conducted in the areas of food chemistry and the chemistry of radiolytic products.

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APPENDIX I

COMMITTEE CHARGE AND RELATED MATERIAL

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Sanford A. Miller, Ph.D. DATE: September 7, 1979
Director, Bureau of Foods HFF-1
Through: Dr. Albert C. Kolbye ACK
Associate Director for Sciences HFF-100

FROM : Herbert Blumenthal, Ph.D.
Director, Division of Toxicology HFF-150

SUBJECT: Establishment of a Committee to review, evaluate, and recommend criteria for safety evaluation of irradiated food.

Need

As you are undoubtedly aware, interest in food irradiation has been increasing recently. The USDA is seriously considering sponsorship of a food irradiation program that is now being conducted by the Army. They see potential for radiation replacing nitrite as a preservative in bacon and possibly other cured meats. There is a significant potential for radiation replacing ethylene oxide and ethylene dibromide, which are currently used as fumigants for fruits and spices. Both fumigants pose toxicological problems. The USDA, the EPA, as well as industry people have contacted us regarding these potential uses.

Although various clearances for irradiated foods have been sought since the 1960s, and although considerable resources have been expended in trying to establish the safe use of irradiated foods, there has been little in the way of positive regulatory response. Instead, petitioners have been frustrated by what they perceive as a continuation of often excessive regulatory requirements and our scientists have been frustrated by what they perceive as poor and inadequate data with which to evaluate safety. In light of what has obviously been a failure in understanding and because of our changing views about toxicologic requirements coupled with the unique problems associated with the toxicologic evaluations of food commodities and the likelihood of increased activity in the Bureau of Foods regarding food irradiation, we recommend that a committee be appointed to reevaluate and determine criteria, consistent with current toxicological knowledge, to assess the safety of irradiated foods.

Reason

In 1958, Congress declared a source of radiation to be a food additive for purposes of the food additives amendment. Early safety studies were based on principles of traditional toxicological testing appropriate for food additives. Two problems

were encountered: food could not be irradiated at high dosages to obtain a safety factor without drastically changing the product; and testing the food itself at mildly exaggerated levels can lead to unphysiological diets.

Many millions of dollars have been spent in the intervening twenty years, particularly by the U. S. Government, to improve the technology and to demonstrate the safety of these irradiated foods. The FDA outlined the type of information needed to demonstrate safety in May 1967. Yet, after all these years of effort only a few minor uses of food irradiation have been approved and those approvals occurred before the 1967 FDA guidelines were issued. The result of most studies was neither a demonstration of safety nor a discovery of potential problems, but another compilation of work whose results could not be conclusively assessed.

Although many of the early failures to achieve regulatory approval of irradiated foods can be attributed to studies which display problems of laboratory performance, more recent studies have suffered from an overwhelming complexity of design. Such changes in experimental design have been made on a more or less ad hoc basis without a full reassessment of the whole range of irradiation and irradiated foods. In light of the new interest in irradiation as a solution to some current food additive and pesticide problems, we feel that it is an appropriate time to reassess whether the requirements for demonstrating safety, outlined in 1967, are the best way of addressing the safety questions consistent with today's knowledge and with the peculiar problems posed by irradiated foods.

Purpose

The purpose of the committee will be to guarantee a full reassessment of all cogent issues applicable to irradiated food. To accomplish this full reassessment, we recommend establishment of a committee of scientists who have not previously played a significant role in development of FDA policy on irradiated food. This committee would profit from the application of a fresh outlook uncolored by the bias of past involvement but at the same time it would be expected to draw on the resources of those people who have had the background and experience for having been deeply involved with FDA irradiated food policy.

Scope

The scope of this committee will be:

1. To review current policy and critical aspects of its past implementation,

2. To examine the foundation and soundness of that policy, and

3. To establish those toxicologic requirements appropriate for assessing the safety of irradiated food consistent with the level of human exposure, where the degree of testing is consistent with the potential risk as predicated on the level of human exposure. These requirements would be analogous to, and consistent with, the philosophy supporting the Cyclic Review of direct additives.

Function

1. To acquaint themselves with the problem by reading appropriate documents, hearing presentations, and questioning persons knowledgeable in this area. (Month 1).

2. To plan an approach for completing the task and submitting it to the Division of Toxicology. (Month 2).

3. To provide a draft report of conclusions to the appropriate Divisions. (Month 6).

4. To submit a final report (May 1980).

Structure

We have designated the following scientists from the Division of Toxicology for this committee:

(1) Dr. Lawrence Valcovic, HFF-170 (Chairman)
(2) Dr. William Greear, HFF-180
(3) Dr. David Hattan, HFF-185

We are also requesting a representative from:

(4) The Division of Chemistry - to address questions on radiolytic products formed and the effect of variables in the process (dose, temperature, air, matrix).

(5) The Division of Nutrition - to address questions on radiation effects on nutrients.

(6) The Division of Food and Color Additives - to assure that all significant issues and resources are identified, and to serve as Executive Secretary. (We understand that Mr. Richard Ronk has designated Dr. Clyde Takeguchi for this role).

We expect the committee will need to draw on the resources of the Division of Microbiology and the Division of Food Technology from time to time, but nothing extensive is anticipated at this time.

Resources

We believe that the complexities and critical nature of this task will require a large commitment of time from persons on this task force, occasionally ranging as high as 50%. It will also require a lesser amount of time from resource people on whom the committee will draw. We expect the need for some monetary assistance to bring in outside consultants with special areas of expertise.

Recommendation

We recommend that authorization be given to appoint this committee and charge the members with their task.

Herbert Blumenthal, Ph.D.

RECOMMENDED COURSE OF ACTION

DECISION

Approved _____ Disapproved _____ Date 9/10/79

Phone

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NUTRITIONAL ADEQUACY

Many of the requirements to demonstrate the nutritional safety and adequacy of an irradiated food that were specified in the 1967 FDA document are still valid and, consequently, remain basically unchanged. New "1980" criteria for the safety evaluation of the nutritional adequacy of irradiated food, as contained in this section, essentially consist of a clarification or expansion of the 1967 document. New general or specific recommendations made elsewhere in this document, which are different from those made by the Division of Nutrition in the 1967 document, supercede the older recommendations or guidelines. Under the current organizational structure within the Bureau of Foods of FDA, assessment of nutritional factors in food additive petitions, including those for irradiated foods, are examined by the Division of Nutrition which is part of the Office of the Associate Director for Nutrition and Food Sciences.

In keeping with one of the functions of the Division of Nutrition, namely, to develop and recommend regulatory approaches to maintain or improve the nutritional quality of the national food supply, any petition for approval of an irradiated food should provide supporting data to demonstrate that the levels of characterizing nutrients, particularly essential nutrients, will be either maintained or improved in comparison to an existing process that the irradiation process would replace. For example, it should be shown that the protein, thiamin, and other key

nutrients in irradiation sterilized beef are comparable to those in a thermally processed product. On the other hand, there would be little concern if an appreciable reduction in vitamin C content were to occur since the product, sterilized beef, contains an insignificant amount of the vitamin and would not normally be regarded by the consuming public as a good source for this particular vitamin. Where there is no appropriate process to serve as a base for comparison, the effects of the petitioned process on the quality of the product will be assessed on a case-by-case basis taking into consideration economic and other factors. These conditions do not, however, diminish the importance of the two-part question in the 1967 document which listed the following as foci with regard to the nutritional aspects of an irradiated food: 1) if a food is an important source of one or more nutrients or nutritional properties or qualities essential for optimum health in any diet, does the proposed irradiation treatment of the food cause it to be adulterated or devalued such that it is nutritionally inferior to the unirradidated food?; and 2) if yes, does it pose a potential public health nutrition risk for individuals in the population? It is to be noted that the first part of the above question would more appropriately involve a comparison, within reason, between an irradiated food and the food treated by a conventional process. This is regarded to be more appropriate than, but should not completely supplant, an evaluation of the nutritional qualities of a food before and after irradiation.

In the 1967 policy statement, nutritional quality was stated to include the following:

1. vitamin content, stability, and physiological availability,
2. fat content, quality and essential fatty acid composition,
3. protein quality,
4. digestibility of fat, carbohydrate, and protein components of a food, and the availability of the potential biological energy derived from them,
5. the absence of anti-metabolites,
6. the absence of toxic degradation products of radiation-sensitive nutrients and nutritional adjuncts (for example, carrageenan, starch, emulsifiers, artificial sweeteners, EDTA), and
7. the subjective qualities of food that make it desirable to eat, such as color, flavor, texture, and masticatory and hunger satisfaction.

These continue to be regarded as appropriate factors for determining nutritional quality with a qualification that an assessment of the absence of the toxic degradation products of radiation-sensitive nutrients and food adjuncts is primarily a matter for toxicological rather than nutritional review.

From a number of studies on the radiation stability of vitamins, protein, fat and other nutrients, it is known that several nutrients are sensitive to ionizing radiation. This sensitivity, however, depends not only upon the nature and composition of the food system, but also on a number of controllable factors such as dose, temperature of the product being irradiated, and the relative presence or absence of oxygen in the

product during irradiation. Hence, the destruction of labile nutrients can be minimized by careful selection of the conditions for irradiation. Several reviews have been published that deal with the effects of irradiation on the nutritional aspects of food[1,2,3]. Some of the macronutrient components - amino acids such as cystine, methionine and tryptophan, for example - are more sensitive to irradiation than others. The amounts that are destroyed, however, are usually insignificant compared to the unirradiated food or to a product treated by a conventional process. Studies with radiation sterilized beef and radiation pasteurized chicken show little or no change in content of specific amino acids, amino acid availability and protein efficiency ratio[1].

Concerns in the past regarding the formation of an antithiamin factor in irradiated food are not supported by recent studies. A report by McGowan and associates[4] indicates that irradiated chicken and thermally processed chicken are equally effective in repleting thiamin-dependent blood enzyme levels in thiamin-deficient rats. Even so, there is ample published evidence that a number of vitamins are labile to some degree when irradiated. Particular attention should be focused on vitamin A and carotene, vitamin E, vitamin C, vitamin B-12, thiamin, and vitamin B-6. Although other vitamins and essential nutrients must not be ignored, the aforementioned vitamins are noted because of published studies that demonstrate losses in irradiated products.

As stated in the 1967 document, a petition should assure that the petitioned radiation process is sound from a nutritional standpoint by satisfactorily demonstrating that the irradiated product is nutritionally safe and efficacious. In that document, an inference was made that compensation for the destruction or alteration of nutritional factors would not be excluded from consideration during a petition review. To make this policy more explicit, restoration of a labile nutrient will be given consideration if the irradiation process has the potential to be highly advantageous for public health, economic, or other reasons such as the extended availability of seasonal or highly perishable products.

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APPENDIX III
HUMAN EXPOSURE

HUMAN EXPOSURE

FACTOR I: FOOD CONSUMPTION FACTORS

Ideally, food consumption factors should be based on the quantity of food actually consumed. Such data are not currently available for most dietary items; however, a recent survey conducted by the United States Department of Agriculture (U.S.D.A.) is now being analyzed by the Division of Nutrition. In the past, U.S.D.A. has published data on food consumption based on retail weights[1] and household surveys[2]. The retail weight food consumption data are calculated from agricultural production figures and estimated loss during distribution. The household survey data are based on personal interviews with household members and reflect food consumption measured at the level at which foods enter the kitchen. Because the household survey data more closely reflect actual consumption than the retail weight data, the household survey data were used to generate Table 1 which is currently in use by the Environmental Protection Agency (EPA) for tolerance setting purposes. This table will be used, in the interim, to estimate the human exposure to irradiated food.

Table I

Average Food Factors

Crop	% diet	lbs/wk/household	grams/person/day
Almonds	0.03	0.03	0.59
Apples	2.53	2.48	50.13
Apricots	0.11	0.11	2.23
Artichokes	0.03	0.03	0.59
Asparagus	0.14	0.14	2.84
Avocados	0.03	0.03	0.59
Bananas	1.42	1.39	28.15
Barley	0.03	0.03	0.59
Beans	2.04	2.00	40.42
Beans,dry edible	0.31	0.30	6.14
Beans,lima	0.19	0.19	3.77
Beans,snap	0.98	0.96	19.44
Beet greens	0.03	0.03	0.59
Beets	0.17	0.17	3.44
Blackberries	0.03	0.03	0.59
Black-eyed peas	0.03	0.03	0.59
Boysenberries	0.03	0.03	0.59
Blueberries	0.03	0.03	0.59
Broccoli	0.10	0.10	2.03
Brussel Sprouts	0.03	0.03	0.59
Buckwheat	0.03	0.03	0.59
Cabbage,sauerkraut	0.74	0.72	14.58
Cantalopes	0.52	0.51	10.33
Carrots	0.48	0.47	9.52
Casabas	0.03	0.03	0.59
Cattle	7.18	7.03	142.37
Cauliflower	0.07	0.07	1.42
Celery	0.29	0.28	5.67
Cheese	1.12	1.10	22.28
Cherries	0.10	0.10	2.03
Chicken	2.58	2.52	51.03
Chicory	0.03	0.03	0.59
Citrus fruits	3.81	3.73	75.54
Cocoa	0.12	0.12	2.38
Coconut	0.03	0.03	0.59
Coffee	0.75	0.73	14.78
Collards	0.08	0.08	1.62
Corn	2.52	2.47	50.02
Corn,pop	0.08	0.08	1.62
Corn,sweet	2.25	2.20	44.55
Cottonseed	0.15	0.15	2.97
Crabapples	0.03	0.03	0.59
Cream	0.13	0.13	2.63
Cranberries	0.03	0.03	0.59
Crenshaws	0.03	0.03	0.59
Cucumbers,inc pickl	0.73	0.71	14.38
Cucumbers,not pickl	0.34	0.33	6.68

Table I (Continued)

Crop	% diet	lbs/wk/household	grams/person/day
Currants	0.03	0.03	0.59
Curcurbits	2.84	2.78	56.30
Damsons	0.03	0.03	0.59
Dates	0.03	0.03	0.59
Dewberries	0.03	0.03	0.59
Eggplant	0.03	0.03	0.59
Eggs	2.77	2.71	54.89
Elderberries	0.03	0.03	0.59
Escarole	0.03	0.03	0.59
Figs	0.03	0.03	0.59
Filberts	0.03	0.03	0.59
Fish,shellfish	1.08	1.06	21.47
ruiting Vegetables	2.99	2.93	59.34
Garlic	0.03	0.03	0.59
Goats	0.03	0.03	0.59
Gooseberries	0.03	0.03	0.59
Grain Crops	13.70	13.41	271.57
Grapefruit	0.99	0.97	19.64
rapes, inc raisins	0.49	0.48	9.72
rapes, not raisins	0.45	0.44	8.91
Greens	0.03	0.03	0.59
Hogs	3.43	3.36	68.04
Honey	0.06	0.06	1.22
Honeydewmelons	0.03	0.03	0.59
Honeyballs	0.03	0.03	0.59
Hops	0.03	0.03	0.59
Huckleberries	0.03	0.03	0.59
Kale	0.03	0.03	0.59
Kohlrabi	0.03	0.03	0.59
Horseradish	0.03	0.03	0.59
Jer Articholes	0.03	0.03	0.59
Kumquats	0.03	0.03	0.59
Leafy Vegetables	2.76	2.70	54.68
Leeks	0.03	0.03	0.59
Lemons	0.17	0.17	3.44
Lentils	0.04	0.04	0.81
Lettuce	1.31	1.28	25.92
Limes	0.17	0.17	3.44
Loganberries	0.03	0.03	0.59
Macadamia nuts	0.03	0.03	0.59
Mangoes	0.03	0.03	0.59
Meat,all	13.65	13.55	274.41
Meat, red	10.81	10.58	214.26
Meat,game	0.09	0.09	1.82
Melons	2.00	1.96	39.69
lk&Dairy Products	28.82	28.00	567.04
Millet	0.03	0.03	0.59
Milo	0.03	0.03	0.59
Molasses	0.03	0.03	0.61
Mushrooms	0.03	0.03	0.59

	lbs/wk/household	grams/person/day
Muskmellons	0.03	0.59
Mustard Greens	0.06	1.22
Nectarines	0.03	0.59
Nuts	0.10	2.03
Oats	0.36	7.09
Okra	0.07	1.42
Olives	0.06	1.22
Onions	0.83	16.40
Onion(dry bulb)	0.72	14.18
Onions,green	0.11	2.23
Oranges	2.17	42.93
Papayas	0.03	0.59
Parsley	0.03	0.59
Parsnips	0.03	0.59
Passion fruit	0.03	0.59
Pawpaws	0.03	0.59
Peaches	0.90	17.82
Peanuts	0.36	7.09
Pears	0.26	5.06
Peas	0.69	13.77
Pecans	0.03	0.59
Peppermint	0.03	0.59
Peppers	0.12	2.43
Persion Melons	0.03	0.59
Pimentos	0.03	0.59
Pineapple	0.30	5.87
Plums,not prunes	0.09	1.82
Plums,inc prunes	0.13	2.63
Pome Fruits	2.79	55.29
Potatoes	5.43	107.54
Poultry	2.94	58.32
Poultry,exc chicken	0.04	0.81
Prunes	0.04	0.81
Pumpkin,inc squash	0.11	2.23
Quinces	0.03	0.59
Radishes	0.03	0.59
Raisins	0.04	0.81
Raspberries	0.03	0.59
Rhubarb	0.05	1.01
Rice	0.55	10.94
Root Crop Veg	11.00	217.91
Rutabagas	0.03	0.59
Rye	0.03	0.59
Safflowwer	0.03	0.59
Salisfy	0.03	0.59
Seed&Pod Veg	3.66	72.50
Shallots	0.03	0.59
Sheep	0.19	3.85
Small Fruit,berries	0.83	16.40
Sorghum	0.03	0.59

Table 4 (Continued)

Crop	% diet	lbs/wk/household	grams/person/day
Soybeans	0.92	0.90	18.19
Spearmint	0.03	0.03	0.59
Spinach	0.05	0.05	1.01
Stone Fruits	1.25	1.22	24.71
Strawberries	0.18	0.18	3.65
Sugar Beet Tops	0.03	0.03	0.59
Sugar,cane&beet	3.64	3.56	72.10
Summer Squash	0.03	0.03	0.59
Sunflower	0.03	0.03	0.59
Sweet Potatoes	0.40	0.39	7.90
Swiss Chard	0.03	0.03	0.59
Tangelos	0.03	0.03	0.59
Tangerines	0.03	0.03	0.59
Taro	0.03	0.03	0.59
Tea	0.07	0.07	1.42
Tomatoes	2.87	2.81	56.97
Turkey	0.33	0.32	6.48
Turnips	0.05	0.05	1.01
Turnip Greens	0.03	0.03	0.59
Walnuts	0.03	0.03	0.59
Water Cress	0.03	0.03	0.59
Watermelon	1.43	1.40	28.35
Wheat	10.36	10.14	205.35
Wintersquash	0.03	0.03	0.59
Youngberries	0.03	0.03	0.59

FACTOR II: DIETARY ITEMS SUBJECT TO IRRADIATION

In the United States only two items are currently approved for irradiation:. wheat and potatoes. In December, 1979, a draft of the Codex Alimentarius Commission's Recommended General Standard For Irradiated Foods proposed that irradiation be approved for certain dietary items. These dietary items and the percent contribution to the diet are listed below in Table II. A variety of dietary items are being tested to determine the feasibility of irradiation as a practical method of food preservation[3]. These dietary items and the percent contribution to the diet are listed in Table III. In the future, irradiation of certain dietary items listed in Table III may not prove to be feasible and thus will not constitute a source of human exposure. However, it appears equally likely that research in the area of food irradiation may demonstrate a need and/or an economic advantage of irradiation as a means of food preservation of other dietary items.

TABLE II. Foods Recommended by Codex for Irradiation

Dietary Item	Percent of the Diet
Potatoes	5.43
Onions	0.83
Papaya	0.03
Strawberry	0.18
Wheat	10.36
Cod and Red Fish	1.08*
Chicken	2.58
Rice	0.55
	21.04 Total

*-Data were available for the category fish and shellfish only; therefore, the figure may be overestimated.

Table III. Other Foods Considered for Irradiation

Dietary Item	Percent of the Diet
Mushroom	0.03
Spices	*
Garlic	0.03
Shallots	0.03
Asparagus	0.14
Cocoa Beans	0.12
Shrimp	*
Endive	*
Mango	0.03
Grain (excluding wheat)	3.34
Beef	7.18
Pork	3.43
Rabbit	*
Dried Fruit	*
Tomato	2.87
Peach	0.90
Apricot	0.11
Cherry	0.10
Raspberry	0.03
Grape	0.45
	18.79 Total

* -Data are not available on these dietary items

FACTOR III: IRRADIATION OF INDIVIDUAL DIETARY ITEMS

Although, wheat and potatoes have received approval for processing by irradiation in the United States, commercial operations for irradiating these dietary items are nonexistent in this country. Therefore, the question arises: To what extent will individual dietary items be subjected to processing by irradiation? For example, mangoes will probably only be irradiated for disinfestation for export purposes. Fresh fish intended for local consumption may not be irradiated; however, fish intended for shipment to other parts of the country may be irradiated in order to extend shelf life. At present, there are no reliable data available to indicate to what extent any individual dietary item will be irradiated. Thus, it is conservatively assumed that if a dietary item is approved for irradiation, the proportion of the diet constituted by that dietary item will be 100 percent irradiated.

In summary, the United States has approved irradiation for two major dietary items constituting approximately 16 percent of the diet, but neither is commercially being irradiated in the United States. The Codex Alimentarius Commission will, in the near future, propose that dietary items representing 21 percent of the diet be approved for irradiation. Taking into account the ever changing dietary habits of the United States population, the various dietary items that could be approved for irradiation, and the percentages of these dietary items which would actually be irradiated, it is difficult to predict, with any degree of

accuracy, the actual amount of irradiated food to which the population will be exposed in the forseeable future. A worst-case estimate would predict that 40 percent of the human diet would consist of irradiated food (Table II plus Table III).

However, from a practical point of view, it is anticipated that the actual human exposure will probably not exceed 10 percent of the diet in the near future. This rough estimate is based on the following factors: 1) many years will be required to develop commerical food irradiation facilities for the mass processing of irradiated foods, 2) not all food approved for irradiation will be irradiated due to economic comparison with other competing techniques used in food processing, e.g. canning and refrigeration and, 3) consumer acceptance of irradiated food versus non-irradiated food is expected to be low, initially, due to the stigma associated with the term "irradiation." A program instituted by the government or private industry in an attempt to educate the public, with respect to the safety of irradiated foods, may encounter considerable resistance on the part of the consumer. Thus, irradiation of major dietary items may not be acceptable as an alternative method of food processing for many years. Irradiation of minor dietary items such as spices may be acceptable to a greater extent than irradiation of major dietary items because of the lower perceived risk involved in their limited use.

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APPENDIX IV

ANIMAL DIET CONSIDERATIONS

DIETARY RECOMMENDATIONS FOR CHRONIC FEEDING STUDIES WITH IRRADIATED FOODS

In those instances where chronic feeding or reproduction studies of an irradiated product prove necessary, it is important to be aware of a number of limitations which are inherent in the performance of chronic studies with irradiated foods. It is very difficult to feed exaggerated amounts of human foods to animals for the purpose of toxicity testing. When a test animal is fed abnormally large amounts of certain foods or macronutrients; e.g., protein or fats, on a chronic basis, the test species become susceptible to nutritional disorders, or organ failure which may in turn result in premature morbidity and/or mortality of the test animals. This particular difficulty is exemplified by chronic feeding studies in the recent past which have substituted up to thirty-five percent of the normal diet with specific irradiated foods; e.g., beef, chicken, potatoes, onion, and papaya. The portion of the diet substituted (35%), did not provide the full complement of nutrients required and, in a number of instances, studies had to be terminated before completion because of premature mortality and/or morbidity.

Instead of merely substituting a portion of the normal diet with a given irradiated food, it is recommended that a new type of dietary regimen be developed. The new regimen would be based upon supplying those food components and amounts as designated by certain published semi-synthetic diets[1]. A balance should be established whereby the test species gets the maximum amount of irradiated food consistent with

satisfaction of nutritional requirments. For example, up to fifteen percent of the rat diet might be protein derived from beef or chicken with small amounts of casein or certain amino acids added to fulfill the required amounts of individual amino acids as described in the semi-synthetic diets[1].

This technique would involve analytically identifying and measuring the various consitutents of a specified food to be irradiated then determining the maximum quantity which might be substituted into the synthetic diet mix, while still supplying all essential nutrients. It would be essential that development of the feeding protocols be carried out with the close consultation and advice of nutritional experts who are experienced at maintaining experimental animals in long-term studies with semi-purified diets[2]. In order to maximize the quantity of irradiated food added to the dietary mix, the foods following irradiation should be freeze-dried (lyophilized).

Lyophilization of the irradiated product will simplify its addition to the diet, since in this form it may be powdered and conveniently mixed with the other dietary components. Furthermore, this dehydration method would have the additional advantage of increasing the stability of the irradiated food (reduced potential for breakdown by microorganisms) and is less destructive than cooking. While it may be suggested that this method will not provide a means of testing volatile radiolytic products, in a practical sense, large amounts of these radiolytic products are lost during packaging, storage or preparation, and thus very small amounts are

consumed. A low level of concern for these radiolytic products is also indicated by the fact that they are present even before packaging, storage or preparation only in the ppb range.

It is important that the semi-synthetic diet be palatable to the species being tested and thus, short-term, pilot feeding studies of the diet should be conducted to determine its acceptance. The caloric density (digestible energy) of the diet must be within the proper range. If the caloric density of the diet of rapidly growing rats is below 2.9 kcal per cubic centimeter of food, the weanling rat cannot meet its energy requirement and its growth rate is impaired[3]. The daily dietary intake of Sprague-Dawley female rats varies dramatically with functional state; i.e., non-pregnant 10 to 15 g, pregnant 20 g and lactating 30 to 35 g. Thus, the dietary demands of the test species will depend upon the type of testing. The nutritional demands of a reproductive or teratogenic study will obviously be different than those of a chronic toxicity study and these differences in nutritional requirements must be considered in the dietary regimen being developed.

Care must be taken to ensure that excessive quantities of food components are not added to the diet. For instance, when rats were provided with a diet which was very high in protein (30 to 50% for 600 days), significant glomerulosclerosis was observed[4]. It is recommended that the following treatment groups be included in reproduction studies with irradiated food products 1) control group on normal laboratory diet, 2) control group on semi-synthetic diet, 3) control group on unirradiated food component supplemented to nutritional requirements by semi-synthetic diet, and 4) test group on irradiated food component supplemented to nutritional requirments by semi-synthetic diet. In other types of toxicity testing; e.g., chronic studies, a normal laboratory diet group may not be required[2].

References

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TESTING

Foods irradiated at doses above 100 Krad and comprising more than 0.01% of the diet are estimated to contain URPs in sufficient quantity to warrant toxicological evaluation. The non-mammalian mutagenicity tests offer a level of sensitivity not practically attainable in whole animal tests, and recalling that many URPs may be similar chemically to substances occurring naturally in foods, these tests are considered appropriate tools to evaluate the potential carcinogenicity of irradiated foods. The tests recommended are 1) gene mutations in bacteria, with and without metabolic activation, 2) gene mutations in cultured mammalian cells, 3) DNA repair in mammalian cells, and 4) recessive lethal mutations in Drosophila. These test are considered to be the minimum battery. Requests for substitutions for any of the above tests should be justified and will be considered on a case by case basis.

Because of the anticipated low level of individual radiolytic products present in the whole irradiated food, the above tests must be performed on extracts in which the concentration of radiolytic products is maximized. Also, many of the radiolytic products from polysaccharides and proteins will be large molecules and will not penetrate the cell membrane in the in vitro systems, hence the use of enzyme digests is recommended prior to the concentration of URPs.

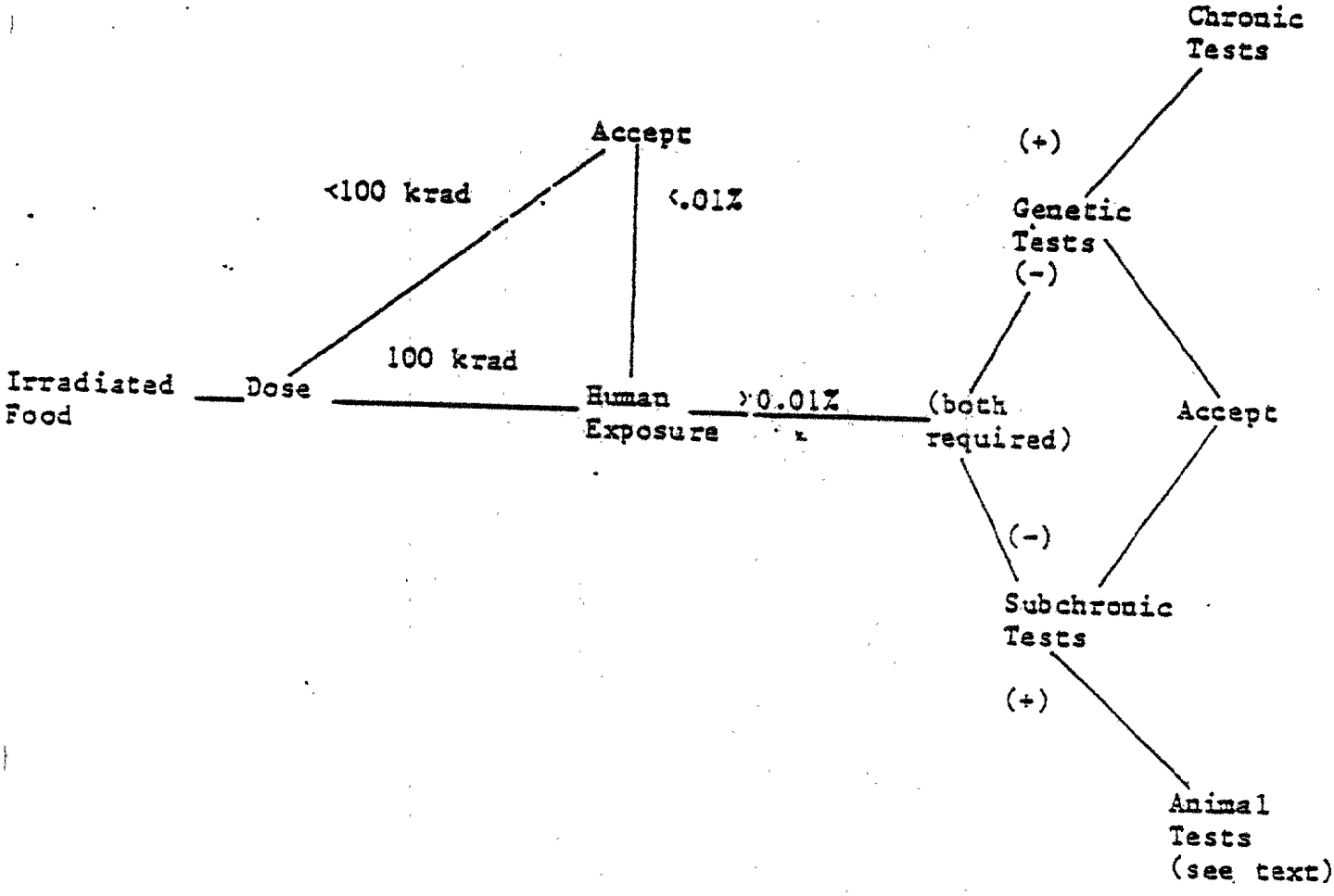
In addition to the short-term mutagenicity tests, foods irradiated at doses above 100 krad must be evaluated in 90-day feeding studies in two species (one rodent, one non-rodent). The 90-day rodent test should include *in utero* exposure. To assure that the test animals are exposed to the highest concentration of radiolytic products possible, the irradiated food may be lyophilized and incorporated into the animal diet at the highest concentration that does not compromise the nutritional requirements of the test species (see Appendix IV). It is not necessary to test enzyme digests of the irradiated food in these tests since each test animal provides digestion of food components before systemic absorption occurs. Higher doses of particular radiolytic products may be obtained if the selectively extracted and concentrated material used in the short-term tests is employed; however, it is recognized that much greater quantities would be needed for *in vivo* testing and thus would make this latter suggestion extremely difficult and expensive to effect in any practical sense.

CRITERIA

Unequivocal negative responses in the required tests will be sufficient to establish the safety of the irradiated food under test. Positive responses obtained in either or both of the types of required tests may trigger additional evaluation. Positive mutagenic responses suggest potential carcinogenicity and hence would necessitiate the performance of the chronic mammalian bioassay tests. The minimal requirements for positive mutagenic effect is the observation of positive responses in at least two of the short-term test systems. The rationale for requiring two positives is to reduce the probability of conducting further tests on the basis of a false positive or a species specific response. The results obtained in the chronic tests would either confirm or negate the positive results obtained in the short-term tests battery regarding the carcinogenic potential of the irradiated food; and, the results obtained in the chronic tests would be considered to be definitive.

In the 90-day studies, a variety of toxicological endpoints are evaluated and it is not possible a priori to determine what follow up tests may be required. Such decisions can only be made upon evaluation of actual test results. If the results obtained from the studies indicate teratological or reproductive effects, then the irradiated food must undergo teratological testing and/or reproductive testing via a three generation reproduction study. The overall procedures for establishing the safety of an irradiated food is displayed in Figure 2.

Figure 2 Safety Decision Tree



GENERIC

The earlier section on radiation chemistry discussed the generalization that the RPs formed are more a function of the chemical composition of the food than the irradiation dose. Thus, foods of a similar chemical composition would be expected to generate structurally similar radiolytic products. Therefore, when two or more foods are of sufficient similarity with respect to both chemical composition (lipids, carbohydrates, proteins and water content) and conditions of irradiation, they may be viewed in a generic sense for regulatory purposes. Comparability of radiation conditions is dependent upon the respective radiation dose, product temperature and ambient atmosphere during irradiation. Hence, toxicologial data obtained from a given irradiated food item may be applicable for another irradiated food in the same generic class. In addition, safety data collected from food irradiated at high doses are applicable to members of the same generic class receiving a lower dose[12].

This generic policy is an extension of the principles set forth in the general policy for evaluating the toxicity of irradiated foods and is based upon the significant research which has been conducted in the areas of food chemistry and the chemistry of radiolytic products.

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